REMARKS

I. Status of the Claims and/or Amendments.

Claims 1-16 are pending in this case and have been examined.

Claims 1-16 were rejected under 35 USC § 112, second paragraph.

Claims 1, 9, and 13 were rejected for lack of positive antecedent basis.

Claims 8, 12 and 13 were rejected for indefiniteness.

Claims 1-7 were rejected under 35 USC § 102 (a)

Claims 1-16 were rejected under 35 USC § 103 (a).

II. Rejections under 35 U.S.C. § 112, paragraph 2 (indefiniteness)

A. Use of the term "Derivatives."

Claims 8, 12 and 16 have been rejected under 35 U.S.C. §112, second paragraph as indefinite in their limitation of the class of contemplated tyrosine kinase inhibitors to "Tyrphostin AG1478 and its derivatives." In particular, the Examiner contends that the phrase "its derivatives" has no particular art recognized meaning, and has not been adequately defined in the specification. *See* Office Action dated June 6, 2001, page 2. Applicants respectfully submit that the term "derivative" does have an art-recognized meaning and that Applicants have used the term in manner wholly consistent with this meaning. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Applicants respectfully draw the Examiner's attention to the fact that the term "derivative" is commonly used in the art when describing various tyrphostins. As an example of how the term is used by those of skill in the art, the Examiner may consult Levitzki, *et al.* "Tyrosine kinase inhibition; an approach to drug development," Science (1995) Vol. 267, pp. 1782-1788. As one can see from Table 2 of the Levitzki, *et al.* article, compounds that are made from a particular precursor are consider to be a "derivative" of that precursor. *See, e.g.*, Table 2

of Levitzki *et al.* (identifying several classes of derivatives (structures M-P, S) of the "BMN" (dihydroxy or dimethoxybenzylidenemalanonitrile compounds (*e.g.*, compounds H for AE17 or AG490)). For example, the "quinoline derivatives" are made via a cyclization reaction of the "CN" group found in the precursor BMN compound. *Id.* (Structure M). Other derivatives involve the addition of particular side chains or groups. *See* Table 2 (N, addition of phosphate group).

As demonstrated by this article, the term "derivative" is used by those skilled in the art to characterize a compound that has been made from a precursor compound, whether by substitution, addition or cyclic condensation. Applicants further note that the foregoing art-recognized meaning of "derivative" is absolutely consistent with their use of the term in the present application. For example, at page 7, line 27 to page 8, line 3, Applicants refer to hydroxystaurospotine as a derivative of staurospotine.

Applicants respectfully submit that the term "derivative" as used in the present claims is not indefinite and, therefore, respectfully request reconsideration and withdrawal of this rejection.

B. Lack of Antecedent Basis.

Claims 1, 9, and 13 have been rejected under section 112, paragraph 2, based on lack of antecedent basis regarding the limitations "the resistance," "the induction" and "the increased rate." Applicants respectfully submit that the claims have been amended to obviate this rejection and respectfully request its withdrawal.

C. Use of the Phrase "Target cell or tissue."

Claims 9 and 13 have been rejected under section 112, paragraph 2, as indefinite for failing to state what it is that targets the recited "target cell or tissue." The Preliminary

Amendment submitted with the Request for Continuing Prosecution Application adopted–with minor editorial changes–the suggestion proposed by the Examiner in the Office Action of February 17, 2000, to overcome this rejection. Accordingly, Applicants respectfully request that the rejection under section 112, paragraph 2, regarding the limitation "target cell or tissue" be withdrawn.

III. Rejections under 35 U.S.C. section 102 (a)

Claims 1-7 have been rejected as being anticipated by Nagane, *et al.*, "*Molecular Mechanisms of Apoptosis Regulation*", Proceedings of AACR Special Conference, January 9-13, 1998. The term "others" in 35 U.S.C. § 102 (a) refers to any entity that is different from the inventive entity. In this case, although the authorship of the abstract includes only three of the present inventors, the work that was presented at the meeting resulted from a collaboration including all five of the listed inventors. Accordingly, the presentation at the meeting was not by "others" as required by 35 U.S.C. § 102(a) and Applicants respectfully request that this rejection be withdrawn.

IV. 35 U.S.C. section 103

Claims 1-16 have been rejected as unpatentable under 35 U.S.C. § 103 over Han *et al.* in view of Reed. Applicants respectfully request reconsideration and withdrawal of this rejection in view of the following remarks.

A. The cited references do not teach all the claim limitations

The present claims require the use of an amount of a tyrosine kinase inhibitor that is effective to modulate resistance to apoptosis. The Examiner cites Han for the proposition that tyrphostin AG1478 is a tyrosine kinase inhibitor that preferentially inhibits tumors that express a

mutant EGFR. The Examiner then cites Reed for the proposition that cisplatin is a known cancer chemotherapeutic agent with the ability to induce apoptosis in cancer cells. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obvious with regard to the present invention since neither cited reference teaches the limitation of an effective amount of a tyrosine kinase inhibitor to modulate apoptosis. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

MPEP §2143.03 reads in pertinent part:

> To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ580 (CCPA 1974).

In the present instance, the art does not provide such limitations. As the Examiner acknowledges, the Han reference does not teach the use of tyrosine kinase inhibitors in combination with apoptosis inducing factors. (Office Action of June 6, 2001, page 4) In fact, the Han reference is silent with regard to any effects of tyrosine kinase inhibitors on apoptosis. The Reed reference does not remedy the deficiencies of the Han reference since it does not address the use of tyrosine kinase inhibitors for any purpose. A word search of the text of the Reed reference shows that it contains neither the word tyrosine nor the word kinase. Clearly, Reed does not teach the use of tyrosine kinase inhibitors to modulate apoptosis. Since there is no teaching in either reference with regard to an effective amount of a tyrosine kinase inhibitor to modulate resistance to apoptosis, the cited references do not teach all the limitations of the present claims. Accordingly, the rejection is improper and should be withdrawn.

B. The combination of the invention has unexpectedly superior properties

The Examiner states that it is well established that combining known compounds with known characteristics is not patentable "where the results obtained thereby are no more than the

additive effects of the ingredients." *citation omitted.* This is an oversimplification of the applicable law. Furthermore, this statement is not applicable to the present facts since the results obtained by the claimed combination is greater than the sum of the results obtained by the individual ingredients. In view of this, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Applicants respectfully draw the Examiner's attention to Figure 6B. The *y* axis is a measure of the percentage of cells that are apoptotic as determined by TUNEL assays. The *x* axis describes the various treatments applied to the cells; these treatments involved combinations of cisplatin and a specified concentration (μM) of one of the following tyrphostins: AG1478, AG1517, AG1479, or AG1536. The (+) and (-) is an indication of the presence or absence of cisplatin (CDDP) respectively. The solid dark bars indicate the percentage of apoptotic cells in the presence of cisplatin while the open bars indicate the percentage of apoptotic cells in the absence of cisplatin. Thus, the open bar is the percentage of apoptotic cells that result from the presence of the tyrosine kinase inhibitor at the indicated concentration.

Applicants respectfully point out that when cisplatin is applied without AG1478–first dark bar from the left–the percentage of apoptotic cells is less than 10 %, approximately 8%. Application of 10 μM of AG1478 without cisplatin provides a barely discernable apoptotic response. Summing the percentage of apoptotic cells expected to result from the combination of cisplatin and 10 μM AG1478 would predict 10% or less of the cells to be apoptotic. Unexpectedly, the actual percentage of cells that are apoptotic as a result of this treatment is approximately 17%, nearly double the expected amount. Treatments of 15 and 20 μM AG1478 without cisplatin result in approximately 2% and 4% apoptotic cells respectively (third and fourth open bars from the left). When these amounts are added to the approximately 8% apoptotic cells caused by cisplatin alone, the expected percentage of apoptotic cells would be approximately 10% and 12% respectively if the results were merely additive. Once again the

observed percentage of apoptotic cells is unexpectedly high. The combination of 15 μM AG1478 and cisplatin results in approximately 24% apoptotic cells–more than double the expected value–while the combination of 20 μM AG1478 and cisplatin results in approximately 25% apoptotic cells–once again more than double the expected value.

These results clearly indicate that the presently claimed methods and compositions have unexpected, superior properties compared to the prior art. In view of this, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

The Examiner is thanked for her cooperation and for her insightful and helpful suggestions.

Applicants submit that the application is in condition for allowance and request early notification of the same. Should the Examiner find that an interview is required to further prosecution of this application, she is invited to telephone the undersigned at her convenience.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17, which may be required, to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R.

§ 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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Dated: December 6, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 1 has been amended as follows:

1. (Thrice amended) A method of modulating an apoptosis-inhibiting effect in a target cell or tissue of a mutant EGFR gene, comprising administering to the cell or tissue an amount of a tyrosine kinase inhibitor that is effective to reduce [~~the~~] resistance to [~~the~~] induction of apoptosis or resistance to an increased rate of apoptosis in the target cell or tissue in combination with a therapy that is effective to induce apoptosis or to increase the rate of apoptosis in the cell or tissue.

Claim 9 has been amended as follows:

9. (Twice amended) A pharmaceutical composition comprising a mixture of:

(A) an amount of an agent that is effective to induce apoptosis or to increase [~~the~~] a rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is effective to reduce resistance to induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR gene, the resistance being mediated by a mutant EGFR.

Claim 13 has been amended as follows:

13. (Twice Amended) A kit for treating cancer comprising:

(A) an amount of an agent that is effective to induce apoptosis or increase [~~the~~] a rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is effective to reduce resistance to induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR gene, the resistance being mediated by a mutant EGFR[~~;~~ ~~(C) wherein said agent and inhibitor may be formulated for either independent or simultaneous administration~~].